Abstract: Human Anti-Amyloid Monoclonal Antibodies Reduce *Salmonella* Typhimurium Biofilm Formation by Targeting Curli

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Bacterial biofilms are frequently associated with human infections and are difficult to eradicate. Furthermore, there is currently no treatment that clears bacterial biofilms formed on medical implant devices, thus colonized devices must be surgically removed at great cost and morbidity to the patient. Amyloids are naturally occurring, insoluble fibrillar proteins defined by a cross-beta sheet secondary structure that is conserved among diverse species throughout nature. One of the best-studied bacterial amyloids is curli, specifically produced by Enterobacteriaceae. Here, we demonstrate inhibition of biofilm formation using human pan-amyloid monoclonal antibodies that target curli of bacterial biofilms. Incubation of *Salmonella enterica* serovar Typhimurium biofilms with human monoclonal anti-amyloid antibodies ALZ.4A6, ALZ.4GI, ALZ.2C10, and ALZ.3H3 during biofilm establishment reduced biofilm thickness and reduced curli content within the biofilm. In comparison to the highly structured biofilms of untreated *S. Typhimurium*, treatment with ALZ.3H3 resulted in the greatest anti-biofilm outcome by inducing a loose three dimensional biofilm architecture where ALZ.3H3 treated biofilms exhibited an increase in height and layers of less densely packed cells. To further investigate the integrity of ALZ.3H3 treated biofilms, we incubated biofilms with fluorescently labeled beads and tracked the bead movement over time using confocal microscopy. In ALZ.3H3 treated biofilms, we observed increased bead penetration in the biofilm as well as greater bead movement throughout the biofilm. ALZ.3H3 disrupted the compact biofilm structure enhancing biofilm eradication by antibiotics and immune cell clearance. ALZ.3H3 was also effective at eradicating preformed biofilms of *S. Typhimurium*. As biofilms are a significant complication associated with implanted medical devices, we explored the ability of ALZ.3H3 to be utilized as an anti-biofilm therapeutic *in vivo*. In *vivo*, treatment with ALZ.3H3 reduced biofilm growth on catheters inserted into the back flanks of mice. ALZ.3H3 injections in combination with antibiotic exposure further enhanced clearance of catheter associated *S. Typhimurium* biofilms. As amyloids are found in the extracellular matrix of both Gram-positive and Gram-negative pathogenic bacteria, including *E. coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, anti-amyloid therapy is a potential strategy for prevention or eradication of biofilm formation by multiple bacterial genera.